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Does living in the Andes make cerebral arteriovenous malformations more dangerous? high altitude fails to predict hemorrhage in a large Ecuadorian cohort

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ABSTRACT

Background: Chronic residence at high altitude (≥2500 masl) induces sustained physiological adaptations in cerebrovascular regulation, including hypoxia-driven angiogenesis, altered hemodynamics, and vascular remodeling. These mechanisms support the hypothesis that lifelong exposure to hypobaric hypoxia in the Ecuadorian Andes could modify the clinical presentation of cerebral arteriovenous malformations (AVMs), although direct evidence remains limited.
Objective: To evaluate whether chronic residence at high altitude is associated with hemorrhagic presentation of cerebral AVMs in adult patients treated at a national tertiary referral center in Quito, Ecuador.
Methods: We conducted an observational, cross-sectional study of 229 adults diagnosed with cerebral AVMs by digital subtraction angiography between 2016 and 2023. Demographic characteristics, residential altitude during early life (first 18 years) and recent adulthood (preceding 10 years), vascular risk factors, AVM intrinsic vascular morphological features, and Spetzler–Martin and Spetzler–Ponce classifications were analyzed. Associations with hemorrhagic presentation at diagnosis were assessed using chi-square or Fisher's exact tests, Student's t-tests, and descriptive modeling. Multivariable regression was explored but not performed due to limited variability in altitude exposure and collinearity among anatomical predictors.
Results: Hemorrhagic presentation occurred in 61.1% of patients. >80% of the cohort resided at high altitude during both exposure periods. No statistically significant association was observed between high-altitude residence, either during early life or recent adulthood, and hemorrhagic presentation ($p > 0.05$). In contrast, intrinsic vascular morphological features showed significant associations with hemorrhage, including deep or subcortical nidus location and higher Spetzler–Martin and Spetzler–Ponce grades ($p < 0.05$). Traditional vascular risk factors, including hypertension and smoking, did not differ between altitude exposure groups.
Conclusion: In this predominantly high-altitude Andean cohort, chronic residence at high altitude was not detectably associated with hemorrhagic presentation of cerebral AVMs. Instead, established intrinsic vascular morphological features remained the dominant predictors of rupture at diagnosis. Given the homogeneity of altitude exposure, these findings likely reflect limited power to detect subtle effects rather than definitive absence of an altitude influence. Multicenter studies with broader altitude variability, physiological markers of hypoxia, and longitudinal follow-up are needed to further clarify the role of environmental hypoxia in AVM natural history.

Abbreviations: AVM, Arteriovenous malformation; VEGF, Vascular endothelial growth factor; CNS, Central nervous system; DSA, Digital subtraction angiography; OR, Odds ratio; masl, meters above sea level; m, meters.

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Introduction

Chronic exposure to high altitude (≥2500 meters above sea level, masl) induces sustained physiological adaptations in cerebrovascular regulation through hypoxia-driven mechanisms.[1] In Ecuador, major Andean cities such as Quito, Cuenca, Ambato, and Riobamba are located at moderate to high altitude, resulting in large populations with lifelong exposure to hypobaric hypoxia.[2] Experimental and clinical studies show that chronic hypoxia upregulates hypoxia-inducible factors and vascular endothelial growth factors (VEGF), promoting angiogenesis, vascular remodeling, and altered permeability in the brain.[3,4] These mechanisms support—though do not establish—a potential influence of prolonged high-altitude residence on the stability of structurally abnormal cerebrovascular networks such as cerebral arteriovenous malformations (AVMs).

Cerebral AVMs are congenital vascular lesions characterized by direct arteriovenous shunting through a dysplastic nidus without an intervening capillary bed.[5] Although relatively uncommon, they represent a leading cause of intracranial hemorrhage in children and young adults, with an estimated annual hemorrhage risk of 2–4% in untreated lesions.[6] Longitudinal population-based studies consistently identify hemorrhagic presentation at diagnosis as the strongest predictor of future bleeding.[7]

Intrinsic vascular morphological features are well-established determinants of hemorrhagic presentation. Deep or infratentorial nidus location increases rupture risk by altering venous drainage and local hemodynamics[8], while intranidal or flow-related aneurysms have been identified as markers of increased hemorrhagic vulnerability.[9] Restricted venous outflow may elevate intranidal pressure and wall stress, contributing to rupture risk, with additional hemodynamic effects occurring at the draining vein–venous sinus junction.[10,11]

The Spetzler–Martin grading system integrates nidus size, eloquence, and venous drainage to stratify surgical risk in AVMs[12], while the Spetzler–Ponce classification condenses this information into clinically actionable categories. However, neither system incorporates environmental or population-level modifiers of vascular biology, such as chronic hypobaric hypoxia.

Environmental hypoxia has been extensively studied in relation to cerebrovascular disease, particularly ischemic stroke, and thrombotic mechanisms.[13] Epidemiologic studies in high-altitude populations demonstrate that altitude influences stroke incidence and cerebrovascular physiology.[14] Developmental studies in Ecuador suggest that hypoxia affects vascular and cardiopulmonary adaptation from early life[15], and genomic and epigenomic analyses of Andean populations reveal altitude-associated modifications in hypoxia-responsive genes involved in vascular remodeling.[16] Despite this evidence, a direct association between chronic altitude exposure and hemorrhagic presentation of cerebral AVMs has not been established.

Recent studies in Ecuadorian and South American high-altitude populations suggest that intrinsic vascular morphology, rather than environmental exposure alone, is the primary determinant of hemorrhagic behavior. In patients with intracranial aneurysms residing at high altitude, angiographic characteristics predict rupture more strongly than demographic or environmental factors.[17] Similarly, in a South American AVM cohort, arterial afferent count correlated with lesion grade but not independently with rupture risk.[18] These findings support a morphology-centered framework for rupture risk assessment in high-altitude populations.

Therefore, this study aimed to evaluate whether chronic residence at high altitude is associated with hemorrhagic presentation of cerebral AVMs in adults treated at a national referral center in Quito, Ecuador. We hypothesized that lifelong exposure to hypobaric hypoxia might modify hemorrhagic presentation risk, while recognizing that intrinsic AVM morphology would remain the dominant determinant of rupture.

Methods

Study design: This research was designed as an observational, cross-sectional study aimed at identifying factors associated with hemorrhagic presentation of AVMs at the time of diagnosis. A cross-sectional approach was selected because AVM rupture status, intrinsic vascular morphological features, and residential altitude history were all ascertained at first clinical presentation, allowing evaluation of associations rather than causal or time-to-event relationships. Although altitude exposure precedes diagnosis temporally, the study design does not permit inference regarding incidence or longitudinal rupture risk.

Setting: The study was conducted at the Eugenio Espejo Specialty Hospital in Quito, Ecuador, a national tertiary referral center located at 2850 masl. As a national referral institution, this center disproportionately evaluates patients with symptomatic, complex, or high-grade AVMs, which may limit generalizability to community-based AVM populations.

Participants: Adult patients (≥18 years) diagnosed with cerebral AVMs between July 2016 and July 2023 were eligible for inclusion. All diagnoses were confirmed by digital subtraction angiography (DSA), ensuring uniform diagnostic accuracy. Patients were required to be born in Ecuador and to have resided continuously within the country to ensure consistent environmental exposure relevant to altitude assessment. Exclusion criteria included age >85 years, AVM rupture secondary to trauma or substance use, and incomplete residential history. These criteria were applied to minimize heterogeneity unrelated to AVM natural history.

Altitude exposure assessment: Residential altitude was assessed using documented place of residence recorded in medical charts and patient interviews at admission. Primary exposure was defined as altitude of residence during the first 18 years of life, reflecting developmental exposure. Secondary exposure was defined as altitude of residence during the 10 years preceding diagnosis, reflecting recent chronic exposure. Altitude was categorized using thresholds commonly applied in high-altitude physiology research, with ≥2500 m defining chronic high-altitude exposure. Additional altitude bins were used to describe geographic distribution but were collapsed for inferential analyses due to sparse cell counts.

Variables and definitions: The primary outcome was hemorrhagic presentation, defined as intracranial hemorrhage attributable to AVM rupture at initial diagnosis. Hemorrhage subtypes -including intraparenchymal, intraventricular, and subarachnoid hemorrhage- were analyzed as a single outcome due to shared rupture mechanism. Covariates included age, sex, self-identified ethnicity, hypertension, smoking status, prior cerebrovascular disease, AVM location, nidus diameter, eloquence, venous drainage pattern, associated aneurysms, and Spetzler–Martin and Spetzler–Ponce classifications.

Angiographic assessment: All angiographic evaluations were performed and graded by a single board-certified neuroradiologist with >10 years of experience. This approach minimized inter-rater variability in AVM characterization.

Statistical analysis: Descriptive statistics were used to summarize demographic, clinical, and angiographic variables. Associations between categorical variables and hemorrhagic presentation were assessed using chi-square or Fisher's exact tests as appropriate based on expected cell counts. Continuous variables were compared using Student's t-test. Multivariable logistic regression was explored but not performed due to limited variability in altitude exposure and collinearity among intrinsic vascular morphological features variables. Accordingly, Fig. 1 is presented as a conceptual model illustrating hypothesized relationships rather than empirical regression output. Statistical significance was defined as $p \leq 0.05$.

Ethical considerations: All procedures adhered to international ethical standards for research involving human subjects. Patient confidentiality was always maintained, with complete anonymization and de-identification of records prior to data processing. The study complied

with the principles outlined in the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice (ICH-GCP) guidelines. The retrospective analysis of prospectively collected clinical data justified post hoc ethics approval. All patient data were anonymized prior to analysis in accordance with the Declaration of Helsinki.

Results

A total of 229 patients with cerebral AVMs were evaluated at the Eugenio Espejo Specialty Hospital between 2018 and 2023. The principal demographic, altitude-related, and anatomical characteristics are summarized in Table 1, Table 2, and Table 3.

Demographic characteristics and altitude exposure

As shown in Table 1, approximately 55% of patients presenting with hemorrhagic presentation were younger than 35 years. No statistically significant differences in age distribution were observed between patients with hemorrhagic and non-hemorrhagic presentation (χ^2, $p > 0.05$). Mean age at diagnosis was similar between groups (35.03±14.17 vs. 32.15±12.74; t-test, $p > 0.05$). Sex distribution was also comparable between groups, with females representing 52.85% of patients with hemorrhagic presentation and 51.89% of those without hemorrhage ($p > 0.05$). Ethnicity was not associated with hemorrhagic presentation. Mestizo patients comprised most of both groups (~65%), followed by Indigenous and Afro-Ecuadorian patients ($p > 0.05$). Traditional vascular risk factors, including hypertension (~20%) and smoking (~25%), were evenly distributed between hemorrhagic and non-hemorrhagic groups. Neither variable demonstrated a statistically significant association with hemorrhagic presentation ($p > 0.05$). Altitude exposure, the central variable of interest, is detailed in Table 3. >85% of patients reported residence at high altitude (≥2500 m) during the first 18 years of life, and nearly 80% resided at high altitude during the 10 years preceding diagnosis. No statistically significant association was observed between high-altitude residence during early life and hemorrhagic presentation ($p > 0.05$). Similarly, recent high-altitude residence was not associated with hemorrhagic presentation ($p > 0.05$). The proportions of patients with and without hemorrhage remained similar across altitude strata.

Anatomic characteristics of AVMs

As summarized in Table 2, subcortical AVMs represented the most frequent location in both hemorrhagic (82.11%) and non-hemorrhagic groups (66.98%). A statistically significant association was observed between AVM location and hemorrhagic presentation (χ^2, $p < 0.05$), although approximately 20% of expected cell counts were below 5. Flow-related aneurysms were identified in >20% of patients in both groups. Neither the presence nor the anatomical type of aneurysm was significantly associated with hemorrhagic presentation ($p > 0.05$). Among patients with associated aneurysms, intranidal lesions were slightly more frequent in the hemorrhagic group (10%), whereas isolated aneurysms predominated among patients without hemorrhage (9.43%). Nidus size did not differ significantly between groups. Small AVMs were most common in both hemorrhagic and non-hemorrhagic patients (54.47% vs. 50.94%), followed by medium-sized (40.65% vs. 37.74%) and large lesions (4.88% vs. 11.32%) ($p > 0.05$). AVMs located in eloquent cortex (37.4% vs. 40.57%) and those with superficial venous drainage (73.17% vs. 64.15%) were similarly distributed between groups and were not associated with hemorrhagic presentation ($p > 0.05$).

AVM grading

In the Spetzler–Martin classification (Table 2), grade II AVMs predominated among patients with hemorrhagic presentation (43.39%), whereas grade I lesions were most frequent among patients without hemorrhage (34.91%). A statistically significant association was identified between Spetzler–Martin grades and hemorrhagic presentation (χ^2, $p < 0.05$). Similarly, the Spetzler–Ponce classification demonstrated a significant association with hemorrhagic presentation. Grade-A lesions accounted for most hemorrhagic cases (67.48%), whereas non-hemorrhagic patients showed a higher proportion of grade-C AVMs (25.47%) ($p < 0.05$). Importantly, high-altitude residence was not associated with higher Spetzler–Martin or Spetzler–Ponce grades. These findings indicate that chronic high-altitude exposure was not associated with increased AVM structural complexity in this cohort ($p > 0.05$).

Fig. 1 shows the conceptual framework for factors associated with hemorrhagic presentation of cerebral AVMs. Fig. 2 displays the

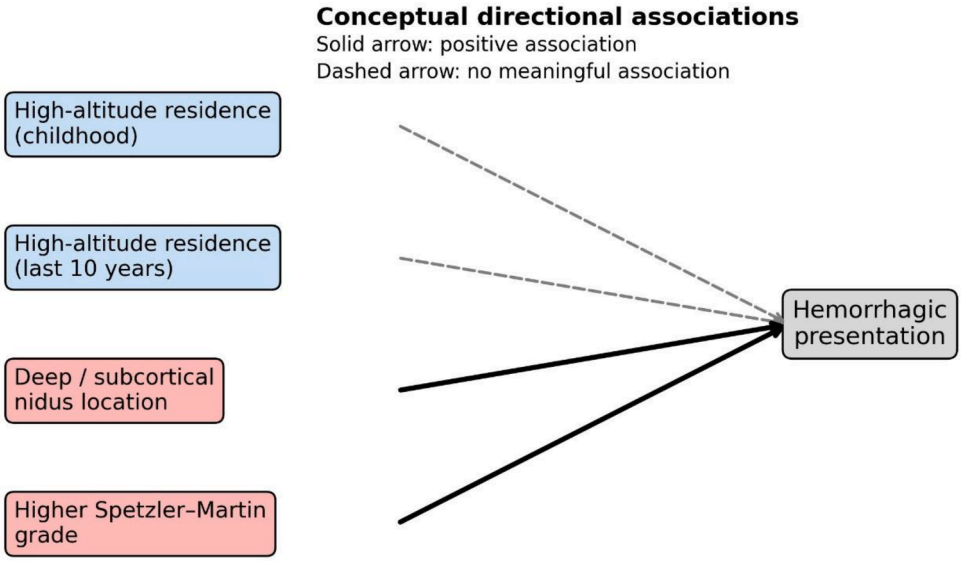

Fig. 1. Conceptual framework for factors associated with hemorrhagic presentation of cerebral AVMs. This schematic Fig. illustrates the qualitative direction of associations between selected clinical and angio-architectural factors and hemorrhagic presentation at diagnosis. Solid arrows indicate variables with a positive association with hemorrhagic presentation, while dashed arrows represent variables with no meaningful association observed in the descriptive analyses. Colors are used to distinguish environmental exposures (blue) from intrinsic angio-architectural features (red). No effect sizes are shown, and the Fig. does not represent results from an executed multivariable regression model.

Table 1
Distribution of 229 patients, according to biological characteristics, history, and frequency of stroke.

Variables		Stroke				Chi-square	$p < 0{,}005$
		Yes		No			
		$n = 123$	%	$n = 106$	%		
Grouped age (years)	< 24	39	31.71	39	36.79	5.708	0.839[a]
	25 a 29	18	14.63	15	14.15		
	30 a 34	13	10.57	14	13.21		
	35 a 39	9	7.32	12	11.32		
	40 a 44	10	8.13	5	4.72		
	45 a 49	10	8.13	6	5.66		
	50 a 54	10	8.13	6	5.66		
	55 a 59	7	5.69	5	4.72		
	60 a 64	2	1.63	2	1.89		
	65 a 69	3	2.44	2	1.89		
	70 a 74	2	1.63	0	0.00		
Age (years)	Ꝑ ± (DS)	35.03 ±	(14.17)	32.15 ±	(12.74)		0.11
Sex	Male	58	47.15	51	48.11	0.021	0.885
	Female	65	52.85	55	51.89		
Ethnicity	Mongrel	80	65.04	69	65.09	2.133	0.344
	Black	10	8.13	4	3.77		
	Native Amerindian	33	26.83	33	31.13		
High blood pressure		25	20.33	21	19.81	0.009	0.923
Tobacco use		31	25.2	29	27.36	0.137	0.712

a: Presence of cells smaller than 5.
Source: Medical records.
Elaboration: authors.

Table 2
Distribution of 229 patients. according to anatomical characteristics of AVM and presence of stroke.

Variables		Stroke				Chi-square	$p < 0.005$
		Yes		No			
		$N = 123$	%	$N = 106$	%		
Anatomical location	Dural	3	2.44	18	16.98	17.18	0.002*[a]
	Pial	4	3.25	6	5.66		
	Subcortical	101	82.11	71	66.98		
	Paraventricular	15	12.2	10	9.43		
	Combined	0	0.00	1	0.94		
Associated aneurysm	27	21.95	22	20.75	0.183	0.663	
Location of the associated aneurysm	Pre-nidal	2	1.63	4	3.77	1.586	0.663a
	Intranidal	13	10.57	8	7.55		
	Isolated	12	9.76	10	9.43		
	Not applicable	96	78.05	84	79.25		
MAV nest diameter (cm)	Small (< 3)	67	54.47	54	50.94	3.264	0.196
	Midfielder (3-6)	50	40.65	40	37.74		
	Large (> 6)	6	4.88	12	11.32		
Eloquent area	46	37.4	43	40.57	0.240	0.624	
Venous drainage	Superficial	90	73.17	68	64.15	2.165	0.141
	Deep	33	26.83	38	35.85		
Spetzler-Martin	Grade I	30	24.39	37	34.91	20.992	<0.001*
	Grade II	53	43.09	20	18.87		
	Grade III	28	22.76	22	20.75		
	Grade IV	8	6.5	18	16.98		
	Grade V	4	3.25	9	8.49		
Spetzler-Ponce	Grade A	83	67.48	58	54.72	9.995	0.007*
	Grade B	28	22.76	21	19.81		
	Grade C	12	9.76	27	25.47		

a: presence of cells smaller than 5; *: statistical significance (<0.05).
Source: Medical records.
Elaboration: authors.

distribution of altitude of residence, demonstrating that >75% of patients in both groups lived above 2500 meters, with no statistically significant differences between stroke and non-stroke patients. Fig. 3 shows the anatomical distribution of AVMs by hemorrhagic presentation.

Discussion

In this study, we evaluated whether chronic residence at high altitude (≥2500 m) is associated with hemorrhagic presentation of cerebral AVMs in an Andean population. Despite strong biological plausibility, no statistically significant association between altitude exposure and hemorrhagic presentation was detected. This finding must be interpreted in the context of marked exposure homogeneity, as >80% of patients in this cohort resided at high altitude during both early life and adulthood.

Chronic hypobaric hypoxia is known to induce cerebrovascular adaptations, including increased cerebral blood flow, altered vascular

Table 3
Distribution of patients diagnosed with AVM. according to residence altitude.

Variables		Stroke				Chi-square	p
		Yes		No			
		N = 123	%	*N* = 106	%		
Residency location until 18 years old (masl)	0 - 100	16	13.01	11	10.38	4.185	0.382a
	100 - 500	0	0.00	1	0.94		
	500 - 1000	11	8.94	7	6.60		
	1000 - 2500	1	0.81	4	3.77		
	>2500	95	77.24	83	78.3		
Residency location in the last 10 years (masl)	0 - 100	15	12.20	10	9.43	3.742	0.442a
	100 - 500	0	0.00	1	0.94		
	500 - 1000	11	8.94	7	6.6		
	1000 - 2500	2	1.63	5	4.72		
	>2500	95	77.24	83	78.3		

a: Presence of cells smaller than 5.
Source: Medical records.
Elaboration: authors.

reactivity, and activation of hypoxia-inducible signaling pathways.[1,2] These physiological responses influence endothelial function and vascular remodeling across multiple cerebrovascular conditions.[3] However, direct evidence linking altitude-related hypoxia to increased fragility or rupture risk of established cerebral AVMs remains limited.

Accordingly, the absence of a statistically significant association in this study should not be interpreted as evidence that altitude has no effect on AVM behavior. Rather, it reflects the inability to detect such an effect within a cohort characterized by limited variability in altitude exposure. Small effective sample sizes in low-altitude strata substantially reduced statistical power to identify modest or context-dependent associations.

In contrast, intrinsic vascular morphological features remained the dominant determinants of hemorrhagic presentation. AVM location and established grading systems showed significant associations with hemorrhage in this cohort. These findings are consistent with large natural history studies, including multicenter observational analyses demonstrating that AVM morphology is the principal driver of rupture risk.[6-8,10]

The overall proportion of hemorrhagic presentation observed in this cohort is comparable to rates reported in major observational AVM series.[6,7] Patients were predominantly young adults, and lesions frequently involved deep or subcortical locations, a pattern commonly described in tertiary referral populations.[5,8]

An important methodological consideration in interpreting these findings is the potential for ecological fallacy. Altitude exposure was measured at the level of geographic residence rather than through individual physiological markers such as oxygen saturation or hemoglobin concentration. As a result, interindividual variability in hypoxic exposure and physiological adaptation could not be captured.[1,15]

Long-term adaptation to high altitude may further mitigate cerebrovascular stress associated with chronic hypoxia. Populations residing in the Andes develop compensatory mechanisms that improve oxygen transport and cerebrovascular resilience over time.[15,16] Such adaptive responses may attenuate any incremental risk that hypoxia could otherwise impose on AVM stability.

Strengths and limitations

A major strength of this study is the use of a relatively large, single-center AVM cohort with uniform angiographic confirmation and consistent lesion characterization, as all imaging was interpreted by an experienced neuroradiologist, reducing interobserver variability.[5,9] The assessment of altitude exposure across two distinct life periods allowed partial consideration of developmental and recent environmental influences. Nevertheless, several limitations must be acknowledged. The cross-sectional design limits causal inference and precludes assessment of longitudinal rupture risk.[7] The marked homogeneity of high-altitude

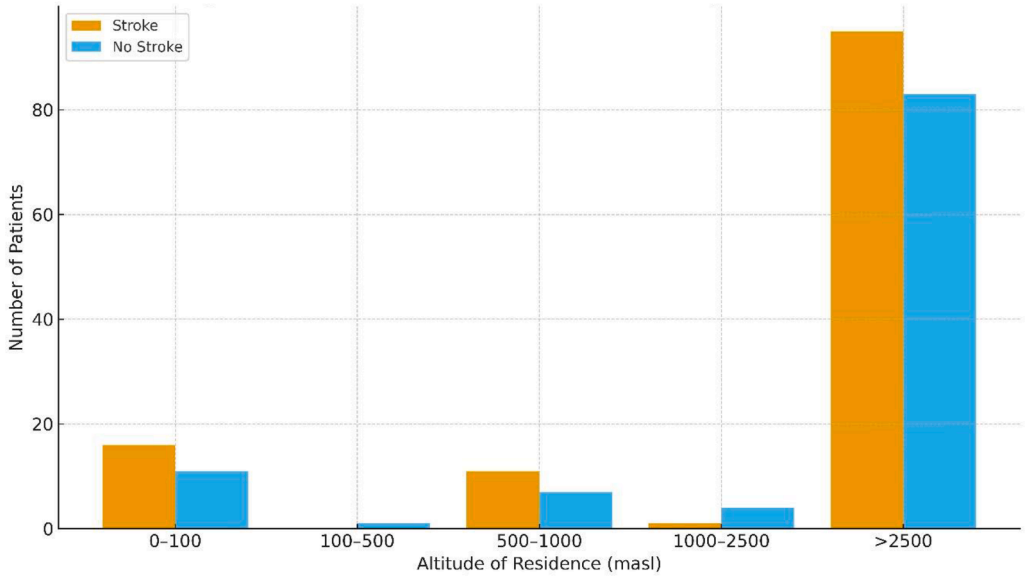

Fig. 2. Altitude of residence and hemorrhagic presentation. Bar plot showing the distribution of patients with and without hemorrhagic presentation of arteriovenous malformations (AVMs) according to altitude of residence during the first 18 years of life. Most patients in both groups resided at elevations >2500 m above sea level, with no significant difference between stroke and non-stroke groups. These findings indicate that lifetime high-altitude residence did not differ between groups and was not associated with hemorrhagic presentation (χ^2 $p > 0.05$).

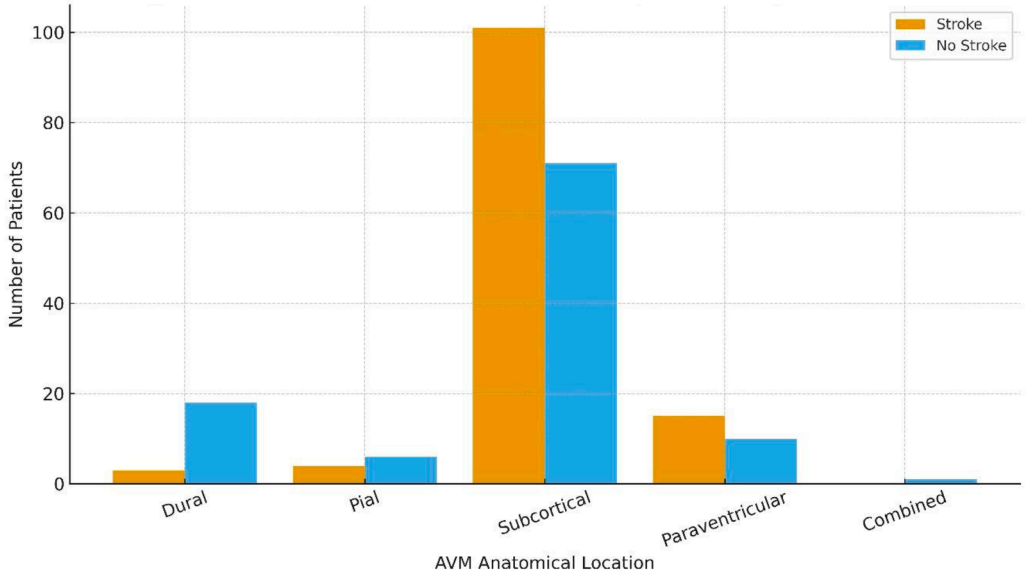

Fig. 3. Anatomical distribution of AVMs by hemorrhagic presentation. Comparison of the anatomical location of AVMs between patients presenting with and without intracranial hemorrhage. Subcortical AVMs were predominant in both groups but occurred more frequently among stroke patients, while dural AVMs were more common in the non-stroke group. A statistically significant association was observed between AVM location and hemorrhagic presentation (χ^2 $p < 0.05$), highlighting the relevance of nidus location as a structural predictor of rupture risk.

exposure substantially reduced statistical power to detect altitude-related effects. Altitude was inferred from residential history rather than individual physiological measures, introducing potential exposure misclassification and ecological bias. Finally, the single-center, tertiary referral setting may overrepresent symptomatic or anatomically complex AVMs, limiting generalizability to population-based cohorts.[5,6] Future studies should prioritize multicenter and multi-altitude designs to increase exposure variability. Integration of quantitative hypoxia metrics, venous hemodynamic assessment, and longitudinal follow-up will be essential to determine whether altitude exerts subtle or modifying effects on the natural history of cerebral AVMs.[17,18]

Conclusion. In this Andean cohort, chronic residence at high altitude was not detectably associated with hemorrhagic presentation of cerebral AVMs. Instead, established intrinsic vascular morphological features remained the principal determinants of rupture at diagnosis. Given the limited variability in altitude exposure, these findings should not be interpreted as evidence of absence of an altitude effect, but rather as the inability to identify such an association within a predominantly high-altitude population. Future multicenter studies incorporating broader altitude ranges, physiological measures of hypoxia, and longitudinal follow-up are needed to clarify whether environmental hypoxia exerts subtle or modifying effects on the natural history of cerebral AVMs.

Declarations

Ethics approval. It was obtained from the Institutional Committee for Academic Review (Comité Institucional de Revisión Académica, CIRA) of Universidad Tecnológica Indoamérica (Approval No UTI-DPS-IRB 033-2025), granted on October 16, 2025.

Consent to participate. Written informed consent was obtained from all participants prior to their inclusion in the study.

Availability of data and materials. The datasets supporting the conclusions of this article are stored by the authors and are available from the corresponding author upon reasonable request.

Competing interests. The authors declare that they have no competing interests.

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Frank David Chamba-Vozmediano: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Germán Abdo-Sarras:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Franz Durán:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Carlos Flores-Enderica:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tatiana Lemos-Garrido:** Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Fabricio González-Andrade:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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